MINIREVIEW

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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 48, pp. 33021–33025, November 28, 2008
Printed in the U.S.A.

Endocannabinoids and the Control of Energy Homeostasis*

Published, JBC Papers in Press, August 11, 2008, DOI 10.1074/jbc.R800012200

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Endocannabinoids (ECBs) are ubiquitous lipid mediators that act through the same G protein-coupled receptors (CB_1 and CB_2) that recognize plant-derived cannabinoids. As regulators of metabolism, ECBs are anabolic: they increase the intake, promote the storage, and decrease the expenditure of energy. Recent work indicates that activation of peripheral CB_1 receptors by ECBs plays a key role in the hormonal/metabolic changes associated with obesity/metabolic syndrome and may be targeted for its pharmacotherapy.

In mammals, body weight and composition are maintained within a narrow range by the integrated control of energy intake, storage, and expenditure. Several important features of this complex regulatory mechanism have emerged as a result of recent advances. First, there are multiple neurotransmitters and hormones involved in regulating energy metabolism with some degree of redundancy. In the case of appetite-promoting (orexigenic) factors, this can ensure energy balance through compensatory changes even if a component is defective, as in the case of neuropeptide Y (1). Second, many of the mediators involved in the neuronal control of appetitive behavior have also been implicated in the regulation of peripheral energy metabolism and vice versa (2, 3). Third, specialized neurons in the brain can sense nutrient availability, and the brain can affect peripheral metabolism indirectly via neural and hormonal mechanisms (4).

What are endocannabinoids (ECBs),[2] and how do they enter this picture? The history of marijuana and its medicinal use go back thousands of years, but the endogenous counterparts of cannabis, the ECBs, have been known for only the last 15 years, their discovery having been triggered by the identification of specific cannabinoid (CB) receptors in the brain (5).

ECBs are endogenous ligands of the same G protein-coupled receptors that recognize plant-derived CBs, or phytocannabinoids, and produce similar biological effects (6). Unlike endogenous opioid peptides, currently known ECBs are fatty acid derivatives, with the two most widely studied ECBs being arachidonoylethanolamide (anandamide), and 2-arachidonoylglycerol (2-AG) (5). Both are generated "on demand" via enzymatic cleavage from membrane phospholipid precursors and are thought to act locally as autocrine or paracrine mediators (6). Their action is terminated by enzymatic degradation, with anandamide being selectively metabolized by fatty acid amidohydrolase (7) and 2-AG being degraded primarily by monoglyceride lipase (8).

Two subtypes of CB receptors have been identified to date. CB_1 receptors (CB_1R) present at very high levels in the brain, but also at much lower yet functionally relevant levels in many peripheral tissues, and CB_2R are expressed primarily by immune and hematopoietic cells (6). Both CB_1R and CB_2R couple to the $G_{i/o}$ subtypes of G proteins, but can also activate additional, G protein-independent pathways (6). In addition, anandamide is a low affinity ligand of TRPV1 (vanilloid) receptors (9). The orphan G protein-coupled receptor, GPR-55, has been shown to bind certain CB analogs, but its physiological functions have not yet been clarified (10).

It is common knowledge that marijuana use improves appetite, presaging the role of ECBs as endogenous orexigenic factors. However, findings as early as the 1970s suggested that Δ^9-tetrahydrocannabinol (THC), the psychoactive ingredient of marijuana, has additional metabolic effects unrelated to appetite. In a hospital-based study, daily smoking of marijuana by healthy volunteers caused an increase in their caloric intake that subsided after a few days, but their weight gain continued throughout the rest of the 3-week study, suggesting independent effects on appetite and metabolism (11). Another early study demonstrated that treatment of healthy humans with THC induces glucose intolerance (12), the importance of which has become clear only recently through the demonstration of the insulin-sensitizing action of the CB_1R antagonist rimonabant in prediabetic human subjects (13). This review briefly summarizes current knowledge about the role of the ECB system in the regulation of energy homeostasis.

Endocannabinoid Regulation of Appetitive Behavior

Soon after the discovery of ECBs and their receptors in the brain, the first potent and selective CB_1R antagonist, SR141716 (rimonabant), was introduced by Sanofi in anticipation of its therapeutic usefulness in a number of conditions, including obesity (14). Indeed, in rodent studies, rimonabant inhibited food intake (15, 16), with preference toward reducing the intake of "palatable" foods (17). This effect was due to the reversal of the tonic orexigenic effect of ECBs, as indicated by its absence in mice lacking CB_1R (18). In the same study, we reported that hypothalamic ECB levels were reduced by leptin and increased in leptin-deficient states, suggesting that orexigenic ECBs are part of the leptin-regulated appetitive neural circuitry and are involved in the hyperphagia and obesity that accompany defects in leptin signaling (18).

A potential site of such a leptin/ECB interaction is neurons in the lateral hypothalamic "hunger center," which express the orexigenic melanin-concentrating hormone. Depolarization of these neurons elicits a CB_1R-mediated suppression of their

* This work was authored, in whole or in part, by National Institutes of Health staff. This minireview will be reprinted in the 2008 Minireview Compendium, which will be available in January, 2009.

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[2] The abbreviations used are: ECBs, endocannabinoids; CB, cannabinoid; 2-AG, 2-arachidonoylglycerol; CB_1R, CB type 1 receptor(s); CB_2R, CB type 2 receptor(s); THC, Δ^9-tetrahydrocannabinol; DIO, diet-induced obesity; FAS, fatty acid synthase.

tonic GABAergic inhibition, which likely accounts for their role in increasing appetite and the ability of CB_1R blockade to decrease it (19). Leptin blocks this depolarization-induced suppression of inhibition by inhibiting voltage-gated calcium channels, resulting in decreased calcium influx and consequently decreased ECB synthesis, a mechanism that contributes to its appetite-suppressing effect (19). These melanin-concentrating hormone neurons project to the ventrolateral tegmental area, the origin of the mesolimbic dopaminergic "reward" pathway. Thus, they represent a functional link between the hypothalamic circuitry controlling consummatory behavior and limbic structures involved in mediating food reward. CB_1R in the medial hypothalamus (20), brainstem (21), and nucleus accumbens (22) have also been implicated in the orexigenic effect of ECBs.

Endocannabinoid Regulation of Energy Metabolism

Early indications that marijuana may influence energy balance through mechanisms unrelated to appetite (see above) were later reinforced by similar findings with ECBs. In both obese and non-obese rats, tolerance to the appetite-reducing effect of chronic CB_1R blockade develops rapidly, whereas the parallel weight reduction is maintained, which must therefore involve an increase in energy expenditure (23). Adult mice deficient in CB_1R are leaner than wild-type littermates due to reduced adiposity, and the difference is maintained upon pair feeding, which excludes the role of altered food intake in the lean phenotype (24). Similarly, $CB_1R^{-/-}$ mice are resistant to high fat diet-induced obesity (DIO) despite similar caloric intake as in wild-type mice, which do become obese on the same diet, again pointing to differences in peripheral energy metabolism (25, 26).

Endocannabinoid Effects in Adipose Tissue

Given the documented involvement of CB_1R in DIO, a likely metabolic target of ECBs is adipose tissue. Indeed, differentiated adipocytes express CB_1R (24, 27, 28) as well as the enzymes involved in ECB biosynthesis and degradation (28), resulting in cellular ECB levels comparable with those in the brain. In primary adipocyte cultures, CB_1R stimulation results in the activation of lipoprotein lipase (24) and decreased expression of adiponectin (29), whereas CB_1R blockade increases adiponectin expression and secretion (27). Both of these targets could contribute to lipid accumulation by providing fatty acids for re-esterification into triglycerides and by reducing fatty acid oxidation, respectively. Chronic CB_1R blockade in mice with DIO was also found to reduce adipose mass through induction of enzymes of fatty acid β-oxidation and the tricarboxylic acid cycle and increased energy expenditure mainly through futile cycling (30).

A reported inverse correlation between fatty acid amidohydrolase expression in adipose tissue and visceral fat mass in obese individuals (31, 32) is also compatible with a lipogenic effect of anandamide, although the underlying mechanisms have not been explored. Additional correlative evidence is the increased adipose tissue ECB content in mice with DIO and in obese humans and a parallel decrease in CB_1R expression in adipose tissue, which may represent down-regulation secondary to increased receptor activation (29). In primary cultured adipocytes isolated from obese Zucker rats, CB_1R expression is increased compared with that in their lean controls (27), which may contribute to the increased efficacy of CB_1R blockade in reducing weight in the obese *versus* lean animals (33). A similar increase in adipocyte CB_1R expression occurs during adipocyte maturation (34), and it may account, in part, for the increased ECB "tone" in obesity.

Although the nature of the primary stimulus that activates the ECB system in obesity is not clear, macrophage infiltration and inflammatory changes in adipose tissue have been implicated in the associated hepatic steatosis and insulin resistance (35–37) and appear to correlate with indicators of increased ECB activity in visceral fat from obese individuals (31). Macrophages are a rich source of ECBs (38), the biosynthesis of which is induced by inflammatory stimuli such as bacterial endotoxin (39) and platelet-activating factor (40). Marijuana can induce glucose intolerance and insulin resistance (12), and chronic daily marijuana use is a risk factor for hepatic steatosis (41). ECBs acting via CB_1R have similar effects, so it is tempting to speculate that macrophage-derived ECBs contribute to the metabolic consequences of obesity.

Adipose tissue lipolysis is under sympathetic nervous system control, whereby norepinephrine released from sympathetic nerve terminals acts at β-adrenergic receptors on adipocytes to activate hormone-sensitive lipase and to suppress adipocyte proliferation. CB_1R are present on peripheral sympathetic nerve terminals, where they mediate inhibition of norepinephrine release (42). ECBs may promote peripheral fat accumulation through this mechanism. Indeed, it has been recently reported that centrally administered leptin suppresses lipogenesis and reduces anandamide content in white adipose tissue, and both effects are abrogated by sympathetic denervation of fat pads. Furthermore, the leptin-induced suppression of adipose tissue lipogenesis was also prevented when the parallel decrease in ECB tone in adipose tissue was compensated by systemic CB_1R activation (43). These findings suggest that suppression of ECB tone is involved in the actions of leptin not only in the hypothalamus, where it contributes to the effect of leptin on appetite (18, 19), but also in adipose tissue, where it may mediate the effect of leptin on lipogenesis (43).

Endocannabinoid Effects on Hepatic Lipid Metabolism

CB_1R are present at low levels in mouse (26, 44–46), rat (47, 48), and human (49) liver, and CB_2R have also been identified in the liver, particularly in profibrotic conditions (50). ECBs are also present in the liver at levels comparable with those found in the brain (26, 51). The potential role of the hepatic ECB/CB_1R system in lipid metabolism is suggested by several lines of evidence. First, *de novo* lipogenesis in the liver is increased in rodent models of high fat DIO (26, 52–54), a paradoxical finding in view of the widely held notion that dietary fatty acids suppress *de novo* lipogenesis. Second, CB_1R-deficient mice are resistant to DIO (25, 26) and the diet-induced increase in hepatic lipogenesis and hepatic steatosis (26). This latter finding could suggest that CB_1R activation promotes *de novo* hepatic lipogenesis and mediates its induction by high fat diets. Third, treatment of wild-type C57BL/6 mice with a potent CB_1

agonist increases the hepatic expression of the lipogenic transcription factor SREBP1c (sterol regulatory element-binding protein-1c) and its targets ACC1 (acetyl-CoA carboxylase-1) and fatty acid synthase (FAS) and also increases *de novo* hepatic lipogenesis, effects that are attenuated by CB_1R blockade and absent in $CB_1R^{-/-}$ mice (26). The presence of similar, CB_1R-mediated lipogenic effects in isolated mouse hepatocytes implicated hepatic CB_1R, although it did not exclude the possible additional involvement of CB_1R in the central nervous system. In a recent study, we reported that mice with selective deletion of CB_1R from hepatocytes do become obese on a high fat diet, but are protected from diet-induced hepatic steatosis, insulin and leptin resistance, and dyslipidemia, which further defines the role of hepatic CB_1R in metabolic regulation (55). CB_1R involvement in hepatic lipogenesis is also indicated by the dramatic reduction of hepatic steatosis by CB_1R blockade in obese Zucker rats (56) and by the finding that daily cannabis use is a risk factor for steatosis severity in people with hepatitis C viral infection (57).

Similar to high fat diets, chronic alcohol intake can also lead to fatty liver due to increased hepatic lipogenesis and decreased elimination of lipids, and recent findings implicate the hepatic ECB/CB_1R system in alcoholic fatty liver (58). The hepatic steatosis induced by feeding mice a low fat/liquid alcohol diet was attenuated by concurrent CB_1R blockade, and mice with global or hepatocyte-specific knock-out of CB_1R were resistant to alcohol-induced steatosis and lipogenic gene expression. These mice also had elevated levels and activity of carnitine palmitoyltransferase-1, the rate-limiting enzyme in fatty acid β-oxidation, which, unlike in controls, were not reduced by ethanol feeding. Ethanol feeding also resulted in up-regulation of CB_1R expression in hepatocytes and a selective increase in the levels of 2-AG in hepatic stellate cells. Co-culture of control (but not CB_1R-deficient) hepatocytes with stellate cells from ethanol-fed mice resulted in up-regulation of CB_1R and lipogenic gene expression in the hepatocytes, which supports a paracrine mechanism whereby stellate cell-derived 2-AG acts on hepatocyte CB_1R to increase *de novo* lipogenesis and to decrease fatty acid oxidation (58). Alcohol or its metabolites did not increase 2-AG levels in isolated stellate cells, suggesting that the *in vivo* effect is mediated indirectly. These findings also reveal a novel function of hepatic stellate cells in inducing steatosis, as illustrated schematically in Fig. 1.

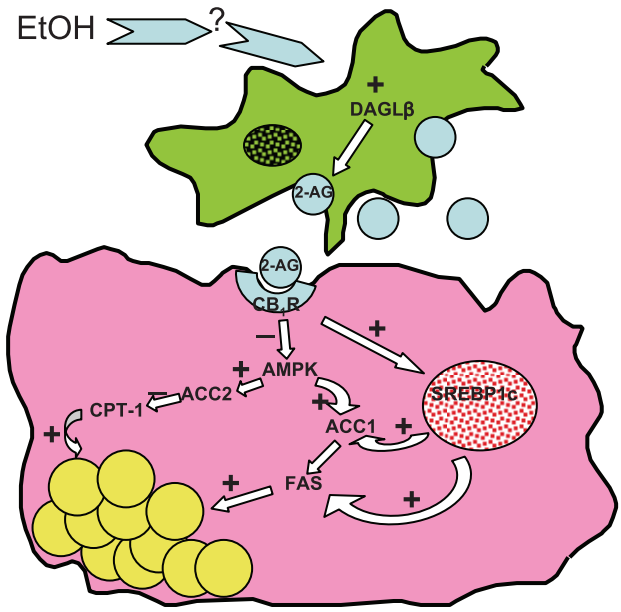

FIGURE 1. **Alcoholic fatty liver involves CB_1R-mediated paracrine induction of hepatic lipogenesis by stellate cell-derived ECB.** Chronic alcohol feeding in mice induces 2-AG production in stellate cells (*green*) by increasing the expression of the 2-AG biosynthetic enzyme diacylglycerol lipase-β (*DAGLβ*). 2-AG activates CB_1R on adjacent hepatocytes (*purple*), which results in increased nuclear expression of SREBP1c and its targets ACC1 and FAS. Activation of CB_1R also inhibits the phosphorylation of AMP kinase (*AMPK*), which results in activation of its targets ACC1 and ACC2, both generating malonyl-CoA. Malonyl-CoA generated by ACC1 then serves as substrate for fatty acid synthesis by FAS, whereas malonyl-CoA generated by ACC2 in the mitochondrial membrane inhibits CPT-1 activity, resulting in reduced fatty acid β-oxidation (for further details, see Ref. 58).

CB_1R Mediate Insulin and Leptin Resistance

Chronic CB_1R blockade in overweight people with the metabolic syndrome results in improved glucose tolerance and insulin sensitivity (13, 59–61), which indicates that the metabolic effects of ECBs are also similar to those of THC (12). When leptin-deficient obese mice were treated daily with rimonabant and then sacrificed to measure glucose handling by skeletal muscle *in vitro*, both glucose uptake and phosphorylation in the presence of 10 nM insulin were increased relative to control preparations from vehicle-treated animals (62). CB_1R are present in skeletal myocytes and are up-regulated in obesity (63) and may be one of the targets for CB-induced insulin resistance and its reversal by CB_1R blockade. The possible involvement of other insulin-sensitive tissues in such effects has not yet been explored. ECBs may also influence insulin secretion in the endocrine pancreas, although there are conflicting reports on CB_1R mediating a decrease (64) or an increase (29) in insulin release. The elevated plasma leptin levels in animals with DIO reflect leptin resistance, and its mediation by CB_1R is indicated by the reduction in plasma leptin levels after chronic CB_1R blockade (65) or by the lower plasma leptin levels in CB_1R-deficient mice on high fat diets (25, 26). Again, the underlying mechanisms have not yet been identified.

Therapeutic Implications

The role of ECBs in increased energy intake and lipogenesis and decreased energy expenditure and their behavioral effects of hypomotility and hypothermia could all be viewed as an evolutionarily conserved system that has favored survival through energy conservation under periods of starvation. Overactivity of the same system under conditions of abundant food and limited physical activity, characteristics of modern societies, results in obesity, hyperlipidemia, and glucose intolerance. This hypothesis has gained strong support from the results of recent clinical trials in which chronic CB_1R blockade in obese individuals with the metabolic syndrome resulted in weight loss and improvements in plasma lipid profile as well as insulin and leptin sensitivity (59–61). An important limitation to the therapeutic application of CB_1R antagonists is that blockade of CB_1R in the central nervous system can cause anxiety and depression in susceptible individuals. Evidence from animal studies indicating that the beneficial metabolic effects are mediated pre-

dominantly via CB_1R in peripheral tissues raises the possibility that peripherally restricted CB_1R antagonists might retain therapeutic efficacy with reduced potential for side effects. Such antagonists are currently being developed, and beyond the potential therapeutic advantage they would offer, their use could also help further define the relative contribution of central *versus* peripheral sites in the various metabolic functions mediated by CB_1R.

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